

Differential arginine dependence and the selective cytotoxic effects of activated macrophages for malignant cells in vitro.

Currie G A; Basham C

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ISSN 0007-0920 Journal Code: 0370635

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Normal and neoplastic cells from 4 species (man, rat, mouse and hamster) were examined for their dependence on exogenous L- **arginine** in tissue culture. The malignant cells **required** a higher concentration of L- **arginine** in the medium than their normal counterparts (with similar doubling times) to maintain optimal proliferation. Complete arginine deprivation resulted in equal growth inhibition of normal and malignant cells, but more rapid cytolysis of the malignant cell. Deprivation of L- **arginine** , followed 24 h later by rescue with L- **arginine** , allowed normal cells to proliferate, but the reproductive capacity of the malignant cells was irreversibly impaired. Since the cytotoxic activity of LPS-activated macrophages was associated with the release of arginase and was abrogated by excess L- **arginine** , it is suggested that the biological basis for the selective effects of such macrophages may reside in the L- **arginine** dependence of the target cells.

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Descriptors: ***Arginine** --metabolism--ME; *Cytotoxicity, Immunologic --drug effects--DE; *Macrophages--immunology--IM; *Neoplasms, Experimental --immunology--IM; Animals; Arginase--metabolism--ME; **Arginine** --pharmacology--PD; Cell Count; Cell Survival --drug effects--DE; Cells, Cultured; Hamsters; Humans; Macrophages--enzymology--EN; Macrophages--metabolism--ME; Mice; Neoplasms...

Chemical Name: **Arginine** ; Arginase

7/3,K,AB/46 (Item 46 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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04256175 PMID: 4840563

Some biochemical considerations in utilization of n

**Inhibition of nitric oxide production in human subjects with
hepatocellular carcinoma or metastatic melanoma by arginine deiminase**

AUTHOR: Logan Theodore F (Reprint); Feun Lynn; Izzo Francesco; Ascierto
Paulo; Ensor C Mark; Holtsberg Frederick W; Bomalaski John S; Clark Mike
A; Curley Steven A

AUTHOR ADDRESS: Indiana University, Indianapolis, IN, USA**USA

JOURNAL: Proceedings of the American Association for Cancer Research Annual
Meeting 44 p1351 July 2003 2003

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Cancer Research Washington, DC, USA July 11-14, 2003; 20030711

ISSN: 0197-016X

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

? s nitric(w)oxide
 307706 NITRIC
 903438 OXIDE
 S1 281477 NITRIC(W)OXIDE
 ? s argine(5n)(deficien? or depriv?)
 161 ARGINE
 700413 DEFICIEN?
 108117 DEPRIV?
 S2 0 ARGINE(5N)(DEFICIEN? OR DEPRIV?)
 ? s arginine
 S3 187312 ARGININE
 ? s s1 and s2
 281477 S1
 0 S2
 S4 0 S1 AND S2
 ? s nitric(5n)(synthase or synthetase)
 307706 NITRIC
 315377 SYNTHASE
 85044 SYNTHETASE
 S5 125840 NITRIC(5N)(SYNTHASE OR SYNTHETASE)
 ? s s1 and s3
 281477 S1
 187312 S3
 S6 68844 S1 AND S3
 ? s s5 and s6
 125840 S5
 68844 S6
 S7 41467 S5 AND S6
 ? s deiminase
 S8 1330 DEIMINASE
 ? s s7 and s8
 41467 S7
 1330 S8
 S9 48 S7 AND S8

? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.

...completed examining records

S10 40 RD (unique items)

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10/3,K,AB/1 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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15048241 PMID: 14599552

Recombinant arginine deiminase as a differential modulator of inducible (iNOS) and endothelial (eNOS) nitric oxide synthetase activity in cultured endothelial cells.

Shen Li-Jiuan; Lin Wen-Chun; Beloussow Karin; Hosoya Ken-Ichi; Terasaki Tetsuya; Ann David K; Shen Wei-Chiang

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Biochemical pharmacology (England) Nov 15 2003, 66 (10) p1945-52, ISSN 0006-2952 Journal Code: 0101032

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Record type: MEDLINE; Completed

Modulation of the extracellular level of **arginine**, substrate for **nitric oxide** synthetases, is a promising modality to alleviate certain pathological conditions where excess **nitric oxide** (NO) is produced. However, complications arise, as only preferential inhibition of the inducible **nitric oxide synthetase** (iNOS), but not endothelial **nitric oxide synthetase** (eNOS), is desired for the treatment of NO over-production. We investigated the effect of **arginine** deprivation mediated by a recombinant **arginine deiminase** (rADI) on the activity of iNOS and eNOS in an endothelial cell line, TR-BBB. Our results demonstrated that cytokine-induced NO production depends on the extracellular **arginine** as substrate. However, if sufficient citrulline is present in the medium, A23187-activated NO production by eNOS does not rely on extracellular **arginine**. Treatment with rADI can markedly inhibit cytokine-induced NO production via iNOS, but not A23187-activated NO production via eNOS. Our results also showed that the decrease of NO production by iNOS could be achieved by depleting **argini**

Recombinant arginine deiminase inhibits nitric oxide production by inducible nitric oxide synthetase , but not endothelial nitric oxide synthetase , in cultured transgenic rat-blood brain barrier endothelial cells.

AUTHOR: Shen Li-Jiuan Margarita (Reprint); Lin Wen Chun; Beloussow Karin Linda; Ann David; Shen Wei Chiang

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JOURNAL: FASEB Journal 17 (4-5): pAbstract No. 398.2 March 2003 2003

MEDIUM: e-file

CONFERENCE/MEETING: FASEB Meeting on Experimental Biology: Translating the Genome San Diego, CA, USA April 11-15, 2003; 20030411

SPONSOR: FASEB

ISSN: 0892-6638 _(ISSN print)

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Arginine , the substrate for nitric oxide synthetases (NOS), is a target in pathological conditions of the cardiovascular system where excess NO is produced. However, complications arise, as only selective inhibition of the iNOS is desired and not of eNOS. We investigated the effect of a recombinant arginine deiminase (rADI) on arginine deprivation, iNOS and eNOS in transgenic rat blood brain barrier endothelial cells. Our results demonstrated that cytokine-induced NO production depends on the extracellular arginine as substrate. However, if sufficient citrulline is present in the medium, A23187-activated NO production by eNOS does not rely on extracellular arginine . The effect of rADI can significantly inhibit cytokine-induced NO production ($p < 0.001$), but not A23187-activated NO production. Thus, rADI appears to be a selective iNOS inhibitor. This is possibly due to the co-localization of eNOS and the arginine regeneration enzymes. Our results also showed that the expression of three arginine -related proteins, iNOS, argininosuccinate synthetase and arginine transporter(s), were up regulated by rADI. Therefore, a decrease of NO production by iNOS in endothelial cells could be achieved by depleting arginine from the medium even under the conditions that would up-regulate iNOS expression. An understanding of rADI-mediated regulation of gene expression can be crucial for treatment of NO over-production.

Recombinant arginine deiminase inhibits nitric oxide production by inducible nitric oxide synthetase , but not endothelial nitric oxide synthetase , in cultured transgenic rat-blood brain barrier endothelial cells.

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411304 Genuine Article#: TB468 Number of References: 21

Title: **MACROPHAGE ACTIVATION BY CULTURE IN AN ANOXIC ENVIRONMENT** (Abstract Available)

Author(s): ALBINA JE; HENRY WL; MASTROFRANCESCO B; MARTIN BA; REICHNER JS

Corporate Source: RHODE ISL HOSP, DEPT SURG, DIV SURG RES, 593 EDDY

ST/PROVIDENCE//RI/02903; BROWN UNIV, SCH MED/PROVIDENCE//RI/02903

Journal: JOURNAL OF IMMUNOLOGY, 1995, V155, N9 (NOV 1), P4391-4396

ISSN: 0022-1767

Language: ENGLISH Document Type: ARTICLE

Abstract: The extracellular amino acid composition of experimental wounds in rats during peak macrophage infiltration bears the imprint of the elevated arginase activity present in wound fluid: L- **arginine** is found in this space in concentrations markedly lower, and L-ornithine in concentrations markedly higher, than those that are detectable in plasma. No evidence, in the form of L-citrulline or NO₂- accumulation, can be found at this time for **nitric oxide synthase** (NOS) activity. Wound-derived macrophages, however, metabolize L- **arginine** through both arginase and NOS in culture. Given the requirements of NOS for O₂ and the reduced O₂ tension in wounds, experiments were performed to determine the role of O₂ availability on the metabolism of L- **arginine** by wound-derived macrophages. Results demonstrated that, beyond inhibiting NOS, culture of wound-derived macrophages in an anoxic environment provided an activation signal, markedly increasing total L- **arginine** metabolism, arginase activity, NOS protein content, and the release of TNF-alpha and IL-6. Neither resident nor *Corynebacterium parvum*-elicited peritoneal macrophages responded to anoxic culture with increases in L- **arginine** utilization, arginase activity or, in the case of resident macrophages, in NOS protein content. The enhanced TNF-alpha and IL-6 release induced by anoxia in wound-derived macrophages was also found in resident peritoneal macrophages. Anoxia appears to act, then, as an inducer of activation-associated traits in macrophages obtained from different sites.

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**haracterization of Mycoplasma arginine deiminase expressed in E. coli
and its inhibitory regulation of nitric oxide synthesis**

AUTHOR: Noh Eun Joo; Kang Sang Wook; Shin Yong Jae; Kim Dong Chung; Park In Sun; Kim Min Young; Chun Boe Gwon; Min Bon Hong (Reprint)

AUTHOR ADDRESS: Department of Pharmacology, College of Medicine, Korea University, Seoul, 136-705, South Korea**South Korea

JOURNAL: Molecules and Cells 13 (1): p137-143 February 28, 2002 2002

MEDIUM: print

ISSN: 1016-8478

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: We previously reported that a cytostatic protein that is found in ASC-17D Sertoli cell-conditioned media was Mycoplasma **arginine deiminase** (ADI), which hydrolyzes L- **arginine** into L-citrulline and ammonia. Here, we report the over-expression of recombinant ADI (rADI) in E. coli and the down-regulation of lipopolysaccharide (LPS) induced- **nitric oxide** (NO) production by rADI treatment. We cloned the ADI gene from Mycoplasma arginini genomic DNA by a polymerase chain reaction, and changed five TGA tryptophan codons (stop codon in E. coli) to TGG codons in the coding region by site-directed mutagenesis in order to express in E. coli. The rADI was purified to apparent homogeneity by DEAE-Sepharose and **arginine** -affinity chromatography. The rADI expressed in E. coli was identified as 45 kDa on SDS-PAGE and 90 kDa on native PAGE, implying that it exists as a dimer like ADI of M. arginini. The Km for **arginine** of rADI was approximately 370+-50 μ M. Its optimal temperature and pH were 41degreeC and pH 6.4, respectively, and enzyme activity remained gtoreq50% for 5 d at physiological temperature and pH. Treatment of purified rADI suppressed NO production in macrophage-like RAW 264.7 and primary glial cells that were exposed to LPS. Furthermore, an intraperitoneal injection of rADI significantly suppressed the rise of blood nitrite/nitrate levels that were induced by the systemic administration of bacterial endotoxin LPS to mice, resulting in an improvement in their survival rate. These results suggest that the depletion of blood **arginine** with an **arginine** -metabolizing enzyme, such as ADI, could suppress excessive production of NO that is caused by inducible NOS (iNOS) during the endotoxemia. Also, rADI may be used as a new approach to control NO-related diseases, such as sepsis.

**Characterization of Mycoplasma arginine deiminase expressed in E. coli
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